Outsourcing Trial Applications

When outsourcing clinical trial applications for submission to EU competent authorities, there are a number of factors for sponsors to consider

Paul Carrodus at TMC Pharma Services

The complexities and national nuances of the competent authority (CA) clinical trial application (CTA) process across EU countries often lead sponsors, especially those based outside the EU, to outsource CA CTA submissions to service organisations within the EU. The decision to outsource gives rise to several items for the sponsor to consider. What outsourcing model will be the best fit? How will trial-related legal requirements be met? Do core trial documents adhere completely to EU guidance? How will the timing of each CA submission fit in with any other planned regulatory activities in the EU? What will be needed for the UK post-Brexit? These considerations need to be addressed in good time to facilitate an efficient submission process and correspondingly rapid approvals for clinical trials.

Outsourcing Models

Each EU regulatory authority has its own specific demands, and sponsors risk considerable delays initiating studies when lacking highly experienced regulatory resources. Specific to the outsourcing of CTAs to EU CAs, a sponsor may decide that CTAs should be outsourced separately to other functional support or that all trial activities should be delegated to a 'full service' company (see Figure 1, page 64). With multiple clinical trials ongoing for an investigational medicinal product (IMP), there is value in using a single service organisation across the full program for CTAs, rather than different organisations per trial (see Figure 2, page 64).

A reason for outsourcing CA CTAs alone may be a sponsor's lack of internal regulatory resources or experience. Equally, the trial design or nature of the IMP may need regulatory approvals that a particular service organisation has experience with. In these circumstances, where all other clinical trial activity can be supported internally or via an additional service organisation, this model can work. It calls for robust vendor oversight by the sponsor, including clearly defined responsibilities for delivering CA CTA documentation and a communication matrix with open communication channels (both between the sponsor and each service organisation, and between service organisations themselves) to facilitate discussion, review, and finalisation of those documents. Outsourcing on a full-service basis comes with the advantage that all necessary liaisons are under one roof. Given the breadth of functional input required for CA CTAs (clinical, pharmacovigilance, medical, quality, etc.), this model offers significant efficiencies. More broadly, having a single-service organisation will reduce the complexity of the sponsor's oversight and the management of its service providers.

Where several trials for a single IMP are running concurrently, there may be other reasons to outsource the CA CTAs on a trial-by-trial basis, e.g., the therapeutic expertise of an organisation or its experience in applications for orphan indications. For a geographically diverse trial, a service company will need to have resources in countries that require applicants to have a local presence and submissions to be made in the local language.

Alternatively, there may be advantages in outsourcing CA CTA activity to a single-service organisation at the programme level: perhaps the organisation has experience with a particular type of IMP (e.g., advanced therapies or stem cells) that may require additional regulatory approvals. Furthermore, having a single organisation providing CA CTA services will make updates to core programme-level documents (such as the investigator's brochure [IB], investigational medicinal product dossier [IMPD], and development safety update reports [DSUR]) more efficient by enabling a single CTA amendment submission to be made for multiple studies running in any given EU country.

EU Legal Representative

Sponsors without presence in the European Economic Area (EU, Norway, Iceland, and Liechtenstein) are required to name an EU legal representative for trials intended to be run in the EU (1). A service organisation can be named as the EU legal representative for a single study or multiple studies. This is most efficient and cost-effective when

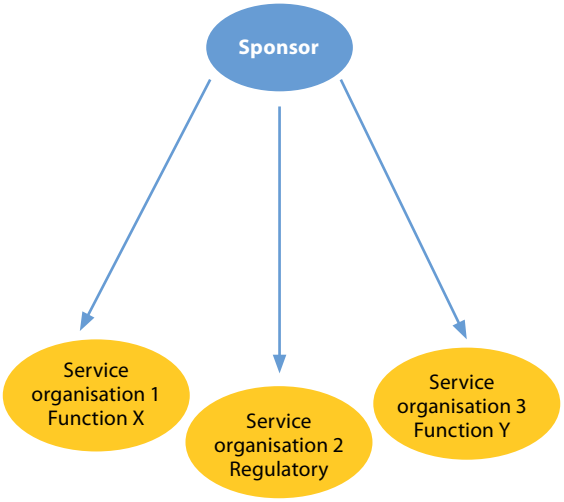

Figure 1a: Functional outsourcing to multiple service organisations

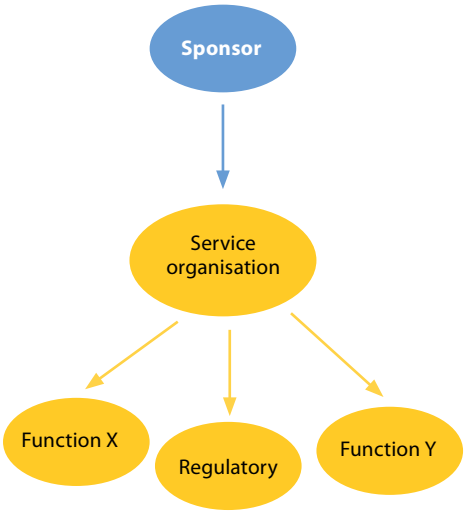

Figure 1b: Full-service outsourcing to a single service organisation

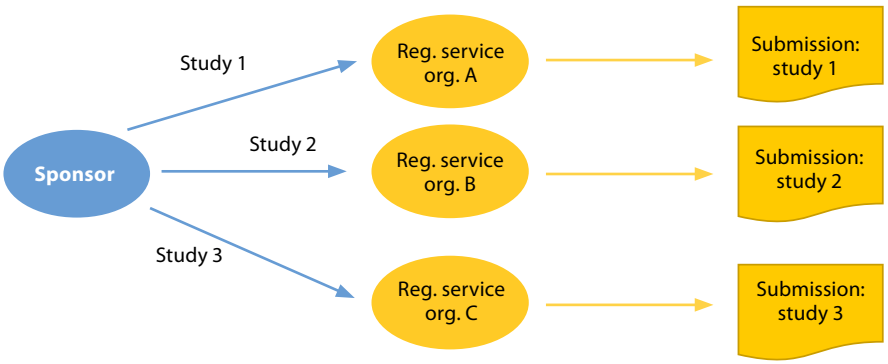

Figure 2a: CA CTA outsourcing at the study level

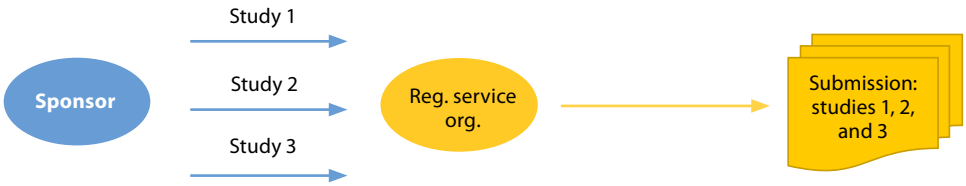

Figure 2b: CA CTA outsourcing at the programme level

provided by the same service company managing the CTAs, and the considerations related to the outsourcing of this service are similar to those for CA CTAs in general.

Submission Route

Sponsors unfamiliar with the options available for submitting CA CTAs should take advice from a service organisation with recent experience across all the different procedures. The recommended route will depend upon trial-specific factors such as the number of EU countries involved in the trial, the nature of the IMP, and the sponsor's intended timelines for enrolment of the first EU patient.

The voluntary harmonisation procedure (VHP) involves a single submission of core CTA documents for a single approval from multiple CAs (2). This is followed by an

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abbreviated national assessment step, prior to full CA approval being issued on a national basis. The key advantage of the VHP is the harmonised assessment of core documents by participating countries, which can work well for studies involving a large number of CAs. Careful resource management is required to ensure availability of the sponsor's subject matter, and experts are necessary to enable rapid responses to any CA questions.

Alternatively, CA CTAs can be submitted on a national basis. While this can represent additional work from a submission standpoint, and may result in divergent comments from CAs on core CTA documents, the approach can pay off in certain EU countries where CA assessment timelines can be relatively quick. The approach also allows for staggered submissions and avoids the 'all-or-nothing' output of the VHP.

Looking ahead, the new EU Clinical Trial Regulation (currently due for implementation during 2021 with a three-year transition period) will introduce a CTA procedure based on a single submission and an assessment procedure with a single EU-wide decision (3-4).

Common Issues

The required format and content of core CA CTA documents, e.g., protocol, IB, IMPD, are subject either in part or in full to EU-specific guidance that CAs will apply during CTA assessment (5). Sponsors unfamiliar with this guidance should work with their service organisation prior to document finalisation, avoiding delays owing to unnecessary CA questions arising during the CTA assessment process.

Deficiencies commonly seen with the protocol include (6):

- Inadequate discussion of potential risks with the IMP, dose-stopping criteria for first-in-human or healthy volunteer trials
- Insufficient consideration of pregnancy and contraception requirements
- Lack of procedures for emergency unblinding
- No clear definition of the end of the trial

A common deficiency of IBs initially written for use outside of the EU is the absence of a reference safety information (RSI) section. The primary purpose of the RSI is to serve as the basis for the 'expectedness' assessments of serious adverse reactions (SARs), by the sponsor for expedited reporting and annual safety reporting of suspected unexpected SARs (SUSARs). Therefore, the RSI should present all 'expected' SARs to the IMP. There may be situations where it is not yet known whether any SARs may be expected (for example, early in clinical development when IMP exposure has been low). In these cases, a clearly defined RSI section of the IB should still be present, followed by a brief text stating that no SARs are yet considered 'expected' by the sponsor for the purpose of expedited reporting and identification of SUSARs in the DSUR (7).

With respect to the chemistry, manufacturing and control, and GMP aspects of CTAs, only sites involved in the manufacturing of EU clinical trial supply should be listed as drug substance or drug product manufacturers in the IMPD. For each EU-based site involved in IMP manufacture, evidence should be provided (in the form of a manufacturing authorisation) that the site is authorised to do so. Activities taking place at manufacturing sites outside the EU must be assessed as conforming to current EU GMP by a qualified person (QP) at the site of EU batch release. This should be evidenced via a signed QP declaration document included in the CA CTA. Frequently, it is the case that a QP will need to conduct a site audit prior to providing this declaration. Sponsors should engage with their QP early to ensure any audits are identified and scheduled in a timely manner to avoid delays to CTA submissions and approvals.

Labelling of IMP must also conform to EU guidance on GMP (annex 13), which describes the information required on both primary and secondary packaging (8). Some EU countries have additional requirements for IMP labelling. Not all CAs require labelling to be included in the CTA, but, for those that do, the proposed labelling text, if not label mock-ups, should be included.

Sequential Regulatory Activities

A sponsor's EU regulatory strategy will be formed of multiple sequential regulatory activities. The timing of these activities, e.g., scientific advice or paediatric investigation plans (PIPs), relative to CA CTAs should be considered to reduce the need for submission of amendments.

EU regulatory scientific advice on data requirements to support CTAs is not mandatory, but, if desired, this should be sought well in advance to allow sufficient time for the advice to be reflected in the CA CTA. A copy of the advice letter or meeting minutes should be included in the application (5). While not binding, nonadherence to advice should be justified in the CTA. Advice from the EMA does not extend to CTAs, but can be sought, for example, on the adequacy of a proposed trial's design to support an eventual EU marketing authorisation application (MAA) or on the use of a novel biomarker that can inform CA CTAs to a certain extent.

For trials that intend to recruit EU patients under the age of 18 and that are being run to support an eventual EU MAA, a sponsor should discuss with its service organisation early in the development of the regulatory strategy whether a PIP is required. In such cases, obtaining PIP approval prior to CA CTA submission is recommended to ensure that the EMA's paediatric development committee's (PDCO's) requirements are taken into account in the final protocol and to establish whether the PDCO sees a need for any prior paediatric formulation or nonclinical development work.

Procedures such as micro, small, or medium enterprise status, orphan drug designation or EMA's priority medicines initiative have little impact on CA CTAs so the timings of such submissions can be uncoupled from the timing of CA CTAs.

Post-Brexit CA CTA Requirements

Sponsors considering running a trial in the UK should be aware of the planned CA CTA requirements in the event of a no-deal Brexit. As is the case now, a CA CTA will need to be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA). Documentation requirements are likely to continue to reflect EU requirements closely, in which case adaptation of a core EU CTA package for use in the UK should be straightforward.

Current MHRA Guidance on a no-deal Brexit suggests that UK CA CTAs will not need to name a UK-based legal representative or site of UK batch release (9). In both cases, MHRA will require legal representatives to be based either in the UK or in a country on an approved list, which would initially include EU countries. However, this MHRA position may change over time, and the EU will certainly continue to require that these activities be conducted from an EU location. With this in mind, while outsourcing these activities, a sponsor should take into consideration whether a service organisation has a presence in both the UK and the EU.

Inadequate or inexperienced internal regulatory resources risk significant issues and delays with CTA approval in the EU; therefore, sponsors frequently consider outsourcing CA CTAs. There are multiple factors to consider in order to ensure a timely and efficient submission process and correspondingly rapid approvals. Only service organisations with extensive breadth and recent experience of CA CTA submissions throughout the EU are able to support non-EU sponsors comprehensively, taking into account EU legislation and guidance as well as national nuances.

References:

1. Visit: ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
2. Visit: www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf
3. Visit: ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
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9. Visit: www.gov.uk/government/collections/mhra-guidance-and-publications-on-a-possible-no-deal-scenario

About the author

Paul Carrodus is Director of Regulatory Services at TMC Pharma Services Ltd. He is a regulatory affairs professional with over 14 years' EU regulatory experience working in major pharma and clinical research organisations. Paul's expertise spans all aspects of regulatory affairs, from early drug development to post-marketing support, including regulatory strategies, MAAs, and lifecycle maintenance support, scientific advice, orphan drug applications, paediatric investigation plans, clinical trial applications, and medical writing.

Email: info@tmcpharma.com